

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

- 5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-25,
 b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-25,

 c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-25, and

- 10 d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-25.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-25.

15

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide of claim 3 selected from the group consisting of SEQ ID NO:26-50.

20

5. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

6. A cell transformed with a recombinant polynucleotide of claim 5.

25

7. A transgenic organism comprising a recombinant polynucleotide of claim 5.

8. A method for producing a polypeptide of claim 1, the method comprising:

- 30 a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

 b) recovering the polypeptide so expressed.

35 9. An isolated antibody which specifically binds to a polypeptide of claim 1.

10. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

- a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:26-50,
- b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:26-50,
- c) a polynucleotide sequence complementary to a),
- d) a polynucleotide sequence complementary to b), and
- e) an RNA equivalent of a)-d).

11. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 10.

12. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 10, the method comprising:

- a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and
- b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

13. A method of claim 12, wherein the probe comprises at least 30 contiguous nucleotides.

14. A method of claim 12, wherein the probe comprises at least 60 contiguous nucleotides.

15. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

16. A method for treating a disease or condition associated with decreased expression of functional EXMAD, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 15.

17. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

18. A pharmaceutical composition comprising an agonist compound identified by a method of claim 17 and a pharmaceutically acceptable excipient.

5

19. A method for treating a disease or condition associated with decreased expression of functional EXMAD, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 18.

10

20. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

15

21. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

20

22. A method for treating a disease or condition associated with overexpression of functional EXMAD, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 21.

23. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 4, the method comprising:

25

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

b) detecting agonist activity in the sample.

18. A pharmaceutical composition comprising an agonist compound identified by a method of claim 17 and a pharmaceutically acceptable excipient.

5

19. A method for treating a disease or condition associated with decreased expression of functional EXMAD, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 18.

10

20. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

15

21. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

20

22. A method for treating a disease or condition associated with overexpression of functional EXMAD, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 21.

25

23. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 4, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

30

35

84/1

AMENDED SHEET

24. An isolated polynucleotide encoding a polypeptide of claim 2.

25. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 10, the method comprising:

- 5
- a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and
 - b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

10 26. A composition of claim 15, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-25.

27. A method of screening for a compound that specifically binds to the polypeptide of claim 1, the method comprising:

- 15
- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
 - b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

20 28. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, the method comprising:

- 25
- a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
 - b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
 - c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity
- 30 of the polypeptide of claim 1.

29. A method of assessing toxicity of a test compound, the method comprising:

- 35
- a) treating a biological sample containing nucleic acids with the test compound,
 - b) hybridizing the nucleic acids of the treated biological sample with a probe

PF-0693 PCT

comprising at least 20 contiguous nucleotides of a polynucleotide of claim 10 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 10 or fragment thereof,

c) quantifying the amount of hybridization complex, and
d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

30. A diagnostic test for a condition or disease associated with the expression of EXMAD in a biological sample, the method comprising:

a) combining the biological sample with an antibody of claim 9, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex, and
b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

31. The antibody of claim 9, wherein the antibody is:

a) a chimeric antibody,
b) a single chain antibody,
c) a Fab fragment,
d) a F(ab')₂ fragment, or
e) a humanized antibody.

32. A composition comprising an antibody of claim 9 and an acceptable excipient.

33. A method of diagnosing a condition or disease associated with the expression of EXMAD in a subject, comprising administering to said subject an effective amount of the composition of claim 32.

34. A composition of claim 32, wherein the antibody is labeled.

PF-0693 PCT

35. A method of diagnosing a condition or disease associated with the expression of EXMAD in a subject, comprising administering to said subject an effective amount of the composition of claim 34.

5 36. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 9, the method comprising:

- a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- 10 b) isolating antibodies from said animal, and
- c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25.

15 37. An antibody produced by a method of claim 36.

38. A composition comprising the antibody of claim 37 and a suitable carrier.

20 39. A method of making a monoclonal antibody with the specificity of the antibody of claim 9, the method comprising:

- a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibody producing cells from the animal,
- 25 c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,
- d) culturing the hybridoma cells, and
- e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of
- 30 SEQ ID NO:1-25.

40. A monoclonal antibody produced by a method of claim 39.

35 41. A composition comprising the antibody of claim 40 and a suitable carrier.

PF-0693 PCT

42. The antibody of claim 9, wherein the antibody is produced by screening a Fab expression library.

43. The antibody of claim 9, wherein the antibody is produced by screening a recombinant immunoglobulin library.

44. A method of detecting a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25 in a sample, the method comprising:

- a) incubating the antibody of claim 9 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25 in the sample.

45. A method of purifying a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25 from a sample, the method comprising:

- a) incubating the antibody of claim 9 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) separating the antibody from the sample and obtaining the purified polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-25.

46. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

47. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:2.

48. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

49. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:4.

50. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5.

51. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID

NO:6.

PF-0693 PCT

68. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:23.

69. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:24.

5 70. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID
NO:25.

10 71. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:26.

72. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:27.

15 73. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:28.

74. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:29.

20 75. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:30.

25 76. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:31.

77. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:32.

30 78. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:33.

79. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:34.

35

84/7

AMENDED SHEET

PF-0693 PCT

80. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:35.

5 81. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:36.

82. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:37.

10 83. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:38.

15 84. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:39.

85. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:40.

20 86. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:41.

87. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:42.

25 88. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:43.

30 89. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:44.

90. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:45.

35 91. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:46.

PF-0693 PCT

92. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:47.

5 93. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:48.

94. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:49.

10 95. A polynucleotide of claim 10, comprising the polynucleotide sequence of SEQ ID
NO:50.